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Comparison of Epinephrine and Vasopressin as Second line Vasopressor in Patients with Septic Shock

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Abstract

Introduction: Septic shock continues to be a significant contributor of ICU mortality. Norepinephrine stands as the primary choice for vasopressor therapy. Either epinephrine or vasopressin is added to norepinephrine or vasopressin to attain the desired mean arterial pressure target. Head-to-head comparisons of these second-line options are scarce. We aimed to compare the effect of epinephrine and vasopressin on 7-day and 28-day mortality, occurrence of acute kidney injury, the duration of mechanical ventilation, as well as the lengths of stay in the ICU and hospital among patients diagnosed with septic shock.

Methodology: Our study included 22 adult patients diagnosed with septic shock who were admitted to the intensive care unit (ICU). When the dose of norepinephrine reached 15 mcg/min, either epinephrine (Group E) or vasopressin (Group V) was added according to the discretion of attending intensivist. Patients were followed-up for a period extending up to 28 days following the initiation of these vasopressors.

Results: In this study of septic shock patients in ICU, epinephrine (n=7) vs. vasopressin (n=15) showed similar 7-day mortality (57% vs. 67%, p=1) and 28-day mortality (0% vs. 7%, p=0.6). While Acute Kidney Injury rates were comparable (71% vs. 47%, p=0.38), epinephrine significantly shortened ventilation (2.8 vs. 5.2 days, p=0.04) and ICU stay (3.2 vs. 5.6 days, p=0.03). Duration of hospital stay remained similar (4.5 vs. 6.4 days, p=0.17).

Conclusion: Administration of either epinephrine or vasopressin as a second line vasopressor has similar effect on 7 and 28-day mortality, incidence of acute kidney injury and the overall duration of hospital stay. Nevertheless, individuals administered with epinephrine experienced a reduced duration of mechanical ventilation and shorter ICU length of stay.

Introduction

Septic shock is defined as sepsis accompanied by hypotension that does not respond with fluid resuscitation.[1] It stands as the primary cause of fatalities in the Intensive Care Unit (ICU) and holds significant importance as a healthcare priority.[2,3] Crucial to the management of septic shock is the prompt initiation of empiric antibiotics, along with resuscitation through fluids and vasopressors.[4,5] Contemporary guidelines for managing septic shock advise the use of norepinephrine

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as the primary vasopressor for adults who fail to reach the target mean arterial pressure (MAP) following initial fluid resuscitation.[1] If norepinephrine proves inadequate in achieving the target mean arterial pressure (MAP), either vasopressin or epinephrine is introduced as an adjunct.[1,5] Studies on head-to-head comparison on outcomes between epinephrine and vasopressin is scarce. A retrospective study indicated no difference in 28-day mortality among patients who were administered either epinephrine or vasopressin.[6]

Our goal was to assess and contrast the impact of epinephrine and vasopressin as second-line vasopressors on the 7-day and 28-day mortality rates in patients with septic shock. Additionally, our secondary objectives included comparing the incidence of acute kidney injury, as well as the durations of mechanical ventilation, ICU stay, and hospital stay.

Methodology

A prospective comparative study was designed to include patients aged 18 years and older who were admitted to the ICU with septic shock at a tertiary care hospital in eastern Nepal.

This study was done from December 2019 to November 2020 in 22 adults consecutively admitted in ICU with septic shock requiring initiation of vasopressor for management of hypotension. Ethical clearance from the Institutional Review Committee, BPKIHS (ref no. Acd/422/077/078), and written informed consent were taken from the patient's relative. Patients transferred from another hospital already on vasopressor, receiving vasopressor other than norepinephrine, with cancer, chronic heart disease (NYHA III/IV) and pregnancy were excluded.

Management of septic shock in all patients adhered to the recommendation by Surviving sepsis campaign.[5] Following the resuscitation with 30 ml/kg of crystalloid within the initial three hours of diagnosing septic shock, if the target mean arterial pressure of 65 mm Hg was not attained, the vasopressor norepinephrine was initiated at a starting dose of 5 mcg/min. Norepinephrine was increased by 2.5 mcg/min every 10 minutes targeting MAP of 65mm Hg to a maximum of 15 mcg/min. Second line vasopressor was started at the discretion of the treating intensivist. Vasopressin was started at 0.6 U/min and was increased by 0.3 U/min every 10 minutes to a maximum of 1.8 U/min. Epinephrine was started and increased in a same dose as norepinephrine. If the target MAP was not achieved using two vasopressors, a third agent was added. Group V received vasopressinwhile Group E receivedepinephrine. Dobutamine was introduced for patients exhibiting a sustained elevation in lactate levels despite sufficient fluid administration and the utilization of vasopressors.. If hemodynamic stability was not achieved using fluid and vasopressors, intravenous hydrocortisone was started at a dose of 50mg/dose 6 hourly (200 mg/day). Resuscitation with fluids, vasopressor and blood was guided to normalize lactate levels if elevated. Patients were followed up extending up to 28 days after the initiation of either epinephrine or vasopressin. The study took note of the 7-dayand 28-day mortality rates, the incidence of acute kidney injury, the length of mechanical ventilation, as well as the durations of ICU and hospital stays. Acute kidney injury was defined as increase in serum creatinine by ≥ 0.3 mg/dl within 48 hours or increase in serum creatinine to ≥1.5 times baseline, or urine volume < 0.5 ml/kg/h for 6 hours.[7]

The principal investigator, who had no role in making management decisions for patients, conducted the data collection. Only the patients were blinded regarding the type of vasopressor used. Gathered data was entered in Microsoft excel 2007 and analyzed using SPSS 11.5 version (IBM SPSS, Inc. Chicago, IL, USA 11.5). Descriptive statistics, including percentage, mean ± SD, median, and interquartile range, were calculated, and the results were presented in tabular form. The normality of quantitative variables was assessed using the Kolmogorov-Smirnov test. For inferential statistics, Chi-square test was employed to examine the mortality differences between the two groups. Mann Whitney test was applied to find the significant difference between demographic and baseline parameter as well as duration of hospital stay, mechanical ventilation and ICU stay at 95% confidence interval where level of significance was < 0.05.

Results

Of 22 patients, 7(32%) received epinephrine and 15(68%) received vasopressin. Age of the patients ranged from 21-77 years. Thirteen (59%) patients were female and 9(41%) were male (Table 1).

Table 1: Demographic and baseline characteristics

Parameters	Group E(n=7)	Group V(n=15)	P value
Sex (M: F)	3:4	6:9	1.0*
	Mean (±SD)	Mean (±SD)	
Age(years)	46.0±21.1	43.07±15.9	0.72**
HR (per min)	131.1±16.2	121.6±14.1	0.17**
RR (per min)	30.2±4.2	28.0±5.9	0.37**
MAP (mm Hg)	53.3±5.7	56.4±4.9	0.21**
Fluid volume before inotropes (ml)		1826.6±393.6	0.33**
APACHE II score	16.5±8.1	21.3±8.3	0.22**

*Chi-square test ** Mann Whitney test

The most common foci for sepsis wasabdomen, which was in 7(46.6%) patients of Group V and 4(57.1%) patients of Group E. Number of patients with 7-dayand 28-day mortality was comparable in both the groups (Table 2).

Table 2: Comparison of outcomes between groups

Parameters	Group E (n=7)	Group V (n=15)	P- value
7-daymortality (No. of patient)	4(57%)	10 (66.6%)	1.0*
28-daymortality (No. of patient)	4(57%)	11(73.3%)	0.6*
Acute kidney injury (No. of patient)	5(71%)	7(47%)	0.38*
	Mean (±SD)	Mean (±SD)	
Duration of mechanical ventilation (mean days)	2.8±1.8	5.2±2.5	0.04**
Duration of ICU stay (mean days)	3.2±1.5	5.6±2.7	0.03**
Duration of hospital stay (mean days)	4.5±1.4	6.4±3.2	0.17**

*Chi-square test **Mann Whitney test.

The average duration of vasopressor support was 13.47 days in group V and 7.29 days in Group-E, (p=0.03). Addition of third vasopressor was required in 5(33.3%) patients of group V and in one (14.2%) patient of group E, (p=0.61).

Discussion

The occurrence of septic shock is steadily on the rise, with approximately 1,500,000 cases of sepsis and septic shock reported annually in North America, and an additional 1,500,000 cases in Europe.[4] The in-hospital mortality rates can be substantial, reaching up to 25-30% for sepsis, and 80% for septic shock.[8] The reported in-hospital mortality rate for patients with septic shock admitted to Asian ICUs stands at 44.5%.[9]

This study aimed to evaluate the impacts of vasopressin and epinephrine as second-line vasopressors in the management of patients with septic shock. The findings reveal that the addition of either vasopressin or epinephrine to norepinephrine has comparable effects on 7-day and 28-day mortality, the incidence of acute kidney injury, and the overall duration of hospital stay. However, it is noteworthy that patients receiving vasopressin exhibited a longer duration of mechanical ventilation and ICU stay compared to those receiving epinephrine.

The surviving sepsis guidelines advocates norepinephrine as primary vasopressor and proposes vasopressin if MAP is inadequate on norepinephrine. Epinephrine is recommended for patients with inadequate MAP on norepinephrine and vasopressin.[10] Very few studies have a direct comparison of these two agents as second line drug in terms of mortality outcome and this study attempted to do so.

In our study, 10 out of 15 patients (66%) in the vasopressin group and 4 out of 7 patients (58%) in the epinephrine group died within 7 days of initiating the second vasopressor. Similarly, 11 patients (73%) in the vasopressin group and 4 patients (53%) in the epinephrine group experienced mortality within 28 days of initiating the second vasopressor. Although the number of patients who died within seven day and 28 days were more in patients receiving vasopressin as compared to epinephrine, the result was not statistically different. Similar reports on mortality were obtained by Menich et al.[11] and Kim et al.[6] However, studies done by Mullner et al.[12] and Hall et al.[13] failed to establish any significant association between vasopressors.

The available data do not conclusively establish a superior survival benefit associated with the use of any specific catecholamine or their combinations in the management of septic shock. Substantial evidence points to individual variations in responses to catecholamines, potentially stemming from differences in volume status, the duration of septic shock, the urgency of its management, phenotypic variations in responsiveness to endotoxin and other inflammatory mediators, coupled with potential downregulation and/or impairment of catecholamine receptors.[14] It has also been postulated that survival of patients with septic shock is dependent on norepinephrine responsiveness. Subsequent requirement of second- and third-line vasopressor agents implies state of non-responsiveness to norepinephrine as well as increasing severity of illness. The restoration of blood pressure may not necessarily lead to improved outcomes in septic shock if the elevated blood pressure is concomitant with a deterioration in cardiac performance, reduced cardiac output, and diminished oxygen delivery.[15] Exceeding mortality rates were observed in patients who administered with higher than 1 μg/kg/min NE in retrospective studies by Brown et al.[16] and Martin et al.[17]

AKI is defined as a rise in serum creatinine by ≥ 0.3 mg/dl within 48 hours, or an increase in serum creatinine to ≥ 1.5 times the baseline, known or presumed to have occurred within the prior 7 days, or a urine volume less than 0.5 ml/kg/h for 6 hours.[7] Seven (out of 15) percent of patients receiving vasopressin and five (out of 7) patients receiving epinephrine developed AKI during their course of treatment in ICU, in our study. However, the result was statistically insignificant.

Improvement in renal function of patients receiving vasopressin for management of hypotension has been reported by Tsuneyoshi et al.[18] However, vasopressin infusion was started very early during the course of management and continued for 16 hours and no comparison was made

between vasopressors. Most of the patients in this study had a very low MAP (mean 55.45 mm Hg) and also had deranged renal function before enrollment in the study and because the increment in blood pressure would by itself increase urine output, lack of association of occurrence of AKI between two groups is reported in our study.

In our study, the duration of mechanical ventilation was notably shorter in patients receiving epinephrine compared to those receiving vasopressin. (p value = 0.046). The total dose of norepinephrine used during the course of treatment in ICU was higher in patients receiving vasopressin compared to epinephrine in our study. Likewise, the overall duration of support with vasopressors was notably longer in the vasopressin group. This could be one of the reasons why the patients in vasopressin group required mechanical ventilation for longer duration. Yamamura et al.[19] also reported reduced duration of mechanical ventilation in patients who were administered lower dosage of norepinephrine. However in a recent large randomized, double-blind, placebo-controlled, multi-center clinical trial (SEPSIS-ACT), performed in patients with septic shock receiving NE, administration of selepressin, compared with placebo, did not increase vasopressor-free days and ventilator-free days within 30 days.[20]

The duration of ICU stay of patients receiving vasopressin was longer compared to patients receiving epinephrine in our study. This is expected as the patients receiving vasopressin required mechanical ventilation for longer duration. Kim et al.[6] documented a comparable duration of ICU stay and ventilator days in patients receiving either vasopressin or epinephrine as a second-line vasopressor for the management of septic shock. Though the duration of ICU stay was comparable in this study, ventilator requirements were more in vasopressin group. Nevertheless, Menich et al.[11] found no disparity in the duration of mechanical ventilation in patients receiving either vasopressin or epinephrine as a second-line vasopressor for the management of hypotension, aligning with the findings in our study.

Limitation: Although statistically insignificant, patients receiving vasopressin stayed in hospital for longer duration as compared to epinephrine in this study.

First, this study lacked a control group. Second, there was discrepancy in the number of patients in two groups. This was likely due to selection bias because the initiation of the second vasopressor was at the discretion of the treating physician. Finally, the sample size was small because the study was halted due to covid 19 pandemic.

Further study can be done in larger population with adding control group. Furthermore, participants and physicians should be blinded to add strength to the study.

Conclusions

The supplementation of either vasopressin or epinephrine to norepinephrine demonstrated comparable effects on seven-day and 28-day mortality, the incidence of acute kidney injury, and the overall duration of hospital stay in patients with septic shock. Nevertheless, patients receiving vasopressin experienced a prolonged duration of mechanical ventilation and ICU stay compared to those receiving epinephrine. Due to the limited sample size, additional research with a larger cohort is necessary to better determine the optimal choice between epinephrine and vasopressin as a second-line vasopressor in patients with septic shock.

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